Chemistry & Biology

In This Issue

In Review: DNA Topoisomerases and Their Poisons

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DNA molecules can assume a number of structural arrangements that pose challenges to transcriptional and replication processes. DNA topoisomerases are enzymes that resolve these topological problems. Given their intimate relationship with DNA and fundamental cellular processes, DNA topoisomerases have emerged as important anticancer and antibacterial drug targets. The review by Pommier et al. now discusses molecular and biochemical properties of these enzymes as well as characteristics and mechanism of action of inhibitors that target them.

In Review: Natural and Artificial Photosynthesis

PAGE 434

Production of storable fuels from light-driven catalysis (solar fuels) is a feasible solution to achieving energy independence and attenuating climate change. Herein, McConnell et al. describe natural photosynthetic systems that produce the solar fuels that power the biosphere and compare them to artificial systems. This comparison effectively informs the study of both natural and artificial photosynthesis to further our understanding of fundamental biological process as well as enable more effective design strategies. Authors emphasize that in the interests of both robustness and efficiency, however, not every aspect of the natural systems should be copied for artificial ones.

From pABA to Coenzyme Q

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Coenzyme Q is a redox active lipid that functions in electron transport chains in cellular membranes and also has an important antioxidant function. Pierrel et al. demonstrate that yeast converts para-aminobenzoic acid (pABA) into Q, making of pABA a new precursor of Q like the long-known 4-hydroxybenzoate. The finding implies that an aromatic NH_2-to-OH conversion occurs to synthesize Q from pABA. The authors identify the reducing system formed by the mitochondrial ferredoxin Yah1p and its reductase Arh1p as essential for yeast Q biosynthesis. Defining whether pABA and the orthologs of Yah1p and Arh1p are involved in mammalian Q biosynthesis is an interesting question and remains to be resolved.

2D-DIGE for Mechanism of Action

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The development of new anticancer agents derived from natural resources requires a rapid identification of their molecular mechanism of action. To enhance the efficiency of this step and accelerate the process, Muroi et al. have initiated the proteomic profiling of HeLa cells treated with the anticancer drugs representing a wide spectrum of mechanisms of action, using proteomic profiling based on two-dimensional difference gel electrophoresis (2D-DIGE). The use of combined data from 19 compounds and cluster analysis allowed their successful classification according to the mechanism of action, suggesting that this strategy could represent a general approach of discriminating between compounds based on their mechanism of action.

p300/CBP HAT Virtual Reality

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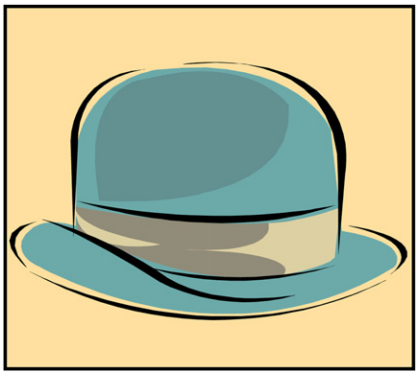

The histone acetyltransferase (HAT) p300/CBP is a pair of transcriptional coactivators with similar structural and functional characteristics. Given the large number of interaction partners, p300/CBP are in the hub of one of the busiest signaling networks, and inhibition of their HAT activity is being currently actively explored as a treatment strategy for number of conditions. Here, Bowers et al. use a structure-based, in silico screening approach and identify a commercially available pyrazolone-containing small molecule, C646, as a p300 HAT inhibitor, with good potency and selectivity. The authors demonstrate that C646 use in cell assays leads to inhibition of histone acetylation and cell growth, suggesting that C646 is a valuable molecular probe and that p300/CBP HAT is a worthy anticancer target.

Viridicatumtoxin and Griseofulvin Gene Clusters

PAGE 483

Filamentous fungi are prolific producers of natural products that have important biological activities. Understanding the enzymatic basis of the biosynthesis of these compounds is therefore an important objective. In this work, Chooi et al. identified and confirmed the biosynthetic pathways of viridicatumtoxin and griseofulvin from *Penicillium aethiopicum*. Viridicatumtoxin is a tetracycline-line compound that has antibiotic activities, while griseofulvin is a classic antifungal agent that has newly discovered anticancer activities. Discovery of these gene clusters provided the basis for genetic and biochemical studies of the pathways.

Morphing 6-Methylsalicylic Acid Synthase into Orsellinic Acid Synthase

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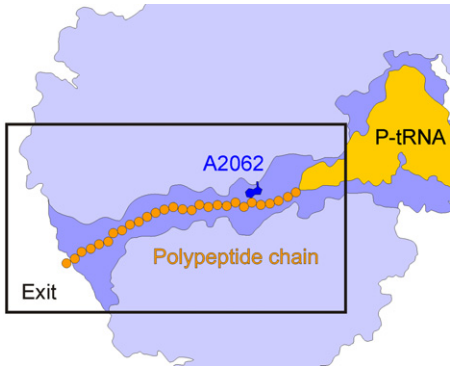
The enzymes 6-methylsalicylic acid synthases (6-MSASs) are involved in the building of an aryl moiety of many bioactive secondary metabolites produced by fungi and bacteria. Given that the ketoreduction is not essential to polyketide chain extension, Ding et al. demonstrate that bacterial 6-MSAS ChlB1 can be engineered to an orsellinic acid synthase, which is compatible to the enzymes for late-stage tailoring in the biosynthesis of spirotetronate antibiotic chlorothricin. The specific protein recognitions facilitate variable aryl group incorporation in making new spirotetronates, which is difficult to achieve by chemical synthesis because of the complexity in architecture, highlighting the significance of this chemoenzymatic strategy.

Ribosomal Exit Tunnel: Macrolides' Playfield



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The clinically important macrolide antibiotics bind within the exit tunnel of the ribosome and inhibit translation by preventing progression of the nascent polypeptide chain. Here, Starosta et al. demonstrate that macrolides exhibit polypeptide-specific inhibitory effects, providing a change to our general mechanistic understanding of macrolide inhibition. Additionally, the authors have utilized amino acid- and peptide-containing macrolides to demonstrate that distinct amino acids and peptides can establish interaction with components of the ribosomal tunnel to enhance the ribosome-binding and inhibitory properties of the macrolide drugs, consistent with the concept that the exit tunnel is not simply a passive conduit for the nascent chain. (Figure credit: Starosta et al.)

Finding the Target in a HCV Genome Haystack

PAGE 515

Hepatitis C virus (HCV) is a positive single-strand RNA virus and a causative agent of hepatitis C, a serious infectious disease affecting the liver. HCV genome represents an emerging target for the design and the development of therapeutic agents. However, the complex structure that viral RNA assumes in the viral particle is a serious obstacle. Sagan et al. developed two methods that interrogate the native folded structure of HCV RNA as tools to predict siRNA potency against HCV RNA. Two methods, a microarray-based approach involving viral RNA microarrays (VRMs) and an HCV viral RNA-coated magnetic bead-based (VRB) assay, predicted potency of the designed siRNAs in cell culture models for HCV replication, which are not easily predicted by informatic means.

Single Cell's Hormonal Response

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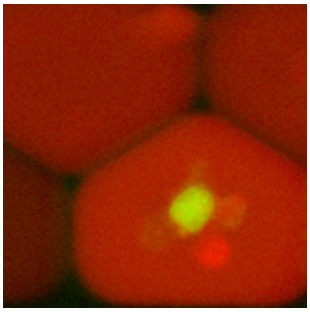
Baret et al. use a droplet-based microfluidic system to perform a quantitative cell-based reporter gene assay for a nuclear receptor ligand. Single *Bombyx mori* cells are compartmentalized in nanoliter droplets together with 8–10 discrete concentrations of 20-hydroxyecdysone, and a fluorescent label encoding the hormone concentration. The simultaneous measurement of the expression of Green Fluorescent Protein by the reporter gene and of the fluorescent label allows construction of the dose-response profile of the hormone at the single-cell level. (Figure credit: Baret et al.)



Small Molecule Oxidative Stress Fighter

PAGE 537

Nrf2 is a transcription factor that controls cellular response to environmental and oxidative stress and regulates expression of various protective enzymes by binding to the antioxidant response element (ARE). Thus, activation of Nrf2 could have significant beneficial cytoprotective effects. Under normal conditions, Nrf2 levels are kept low via proteasomal degradation mediated by an E3 ubiquitin ligase complex, Cul3, and an adaptor protein, Keap1. Hur et al. now identify a small molecule ARE-activator, named AI-1, and establish that it activates Nrf2 by covalently modifying Keap1 at Cys151. This modification inhibits Keap1 adaptor activity and leads to stabilization and transcriptional activation of Nrf2.

